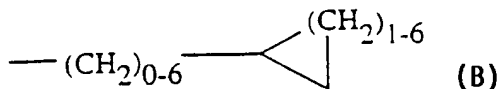
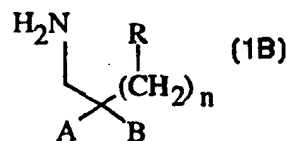
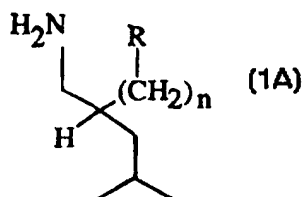




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 257/04, A61K 31/41, C07D 271/06, C07F 9/38, A61K 31/66, C07D 291/04		A3	(11) International Publication Number: WO 99/31074
			(43) International Publication Date: 24 June 1999 (24.06.99)
(21) International Application Number: PCT/US98/23917		(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.	
(22) International Filing Date: 10 November 1998 (10.11.98)			
(30) Priority Data: 60/069,773 16 December 1997 (16.12.97) US 60/104,924 20 October 1998 (20.10.98) US		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(72) Inventors; and (75) Inventors/Applicants (for US only): BELLIOTTI, Thomas, Richard [US/US]; 6125 Lodi Lane, Saline, MI 48176 (US). BRYANS, Justin, Stephen [GB/GB]; Dean Cottage, 3 W. Wickham Road, Balsham CB1 6DZ (GB). CAPIRIS, Thomas [US/US]; 14816 Greenbriar Court, Plymouth, MI 48170 (US). HORWELL, David, Christopher [GB/GB]; 8 West Hill, Foxton, Cambridge CB2 6SZ (GB). KNEEN, Clare, Octavia [GB/GB]; Slade Cottage, Petts LN, Little Walden, Essex CB10 1XH (GB). WUSTROW, David, Juergen [US/US]; 5101 John Holmes Road, Ann Arbor, MI 48103 (US).		(88) Date of publication of the international search report: 4 November 1999 (04.11.99)	

(54) Title: ((CYCLO)ALKYL SUBSTITUTED)-GAMMA-AMINOBUTYRIC ACID DERIVATIVES (=GABA ANALOGUES), THEIR PREPARATION AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISORDERS



(57) Abstract

Novel amines of formulas (1A) and (1B) or a pharmaceutically acceptable salt thereof wherein: n is an integer of from 0 to 2; R is sulfonamide, amide, phosphonic acid, heterocycle, sulfonic acid, or hydroxamic acid; A is hydrogen or methyl; and B is (a), straight or branched alkyl of from 1 to 11 carbons, or $-(CH_2)_{1-4}-Y-(CH_2)_{0-4}$ -phenyl wherein Y is -O-, -S-, -NR', wherein R' is alkyl of from 1 to 6 carbons, cycloalkyl of from 3 to 8 carbons, benzyl or phenyl wherein benzyl or phenyl can be unsubstituted or substituted with from 1 to 3 substituents each independently selected from alkyl, alkoxy, halogen, hydroxy, carboxy, carboalkoxy, trifluoromethyl, and nitro are disclosed and are useful as agents in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, inflammatory diseases, and gastrointestinal disorders, especially IBS. Processes for the preparation and intermediates useful in the preparation are also disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/23917

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D257/04 A61K31/41 C07D271/06 C07F9/38 A61K31/66
C07D291/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2 465 803 A (HEATH R.L. & PIGGOTT H.A.) 29 March 1949 see reduction products of examples 4,5,7-9,11,12 ---	1
X	US 2 866 786 A (FEICHTINGER H. & TUMMES H.) 30 December 1958 see column 3, line 50 - line 52 ---	1
X	RIEMSCHNEIDER R. & KAMPFER H.: "Zur Kenntnis der cis-trans-Asymmetrie. XI. Optische Aktivität von cis,trans-1,3-Bis-[.alpha.-phenylcinnamoyl amino]-2-methyl-2-n-propyl-propan" JUSTUS LIEBIGS ANNALEN DER CHEMIE, vol. 665, 1963, pages 35-42, XP002098848 see formula VIII see page 37 --- -/--	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

1 April 1999

Date of mailing of the international search report

23. 09.99

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hartrampf, G

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/23917

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>MARKOV V.I. & BURMISTROV S.I.: "1-(Arylsulfonyl)-2,2-dimethylaziridines. II. Reactions with ammonia amines, arenesulfonamides, and phthalimide" THE JOURNAL OF GENERAL CHEMISTRY, USSR, vol. 35, no. 1, January 1965, pages 158-161, XP002098849 see formula I see section experimental, first and second compound see page 159</p> <p>---</p>	1
X	<p>BOSNICH B. & DWYER F.P.: "Mixed bidentate and tridentate complexes of cobalt" AUSTRALIAN JOURNAL OF CHEMISTRY, vol. 19, 1966, pages 2045-2050, XP002098850 see page 2050, paragraph 2</p> <p>---</p>	1
X	<p>VINOT N.: "No. 683. Synthèse de cyanométhyl-2 benzimidazoles .alpha.-substitués. Leur utilisation à la préparation de benzimidazoles possédant d'autres fonctions" BULLETIN DE LA SOCIÉTÉ CHIMIQUE DE FRANCE, no. 12, 1966, pages 3989-3993, XP002098851 see formula 4 see second compound see page 3992, column 2</p> <p>---</p>	1
X	<p>TENTHOREY P.A. ET AL.: "New antiarrhythmic agents. 3. Primary .beta.-amino anilides" JOURNAL OF MEDICINAL CHEMISTRY, vol. 22, no. 10, October 1979, pages 1182-1186, XP002098852 see compounds 35 and 36 see page 1184; table II</p> <p>---</p>	1
X	<p>FOKIN A.V. ET AL.: "The fluoroacylation of diamines" BULL. ACAD. SCI. USSR, DIV. CHEM. SCI., vol. 30, no. 4, April 1981, pages 643-646, XP002098853 see formulae IIIa and VI see page 644; table 1</p> <p>---</p>	1
X	<p>EP 0 061 673 A (ASAHI KASEI KOGYO KABUSHIKI KAISHA) 6 October 1982 see example 15; tables 9-1</p> <p>---</p>	1
	<p>---</p> <p>-/--</p>	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 103, no. 15, 14 October 1985 Columbus, Ohio, US; abstract no. 122998x, "Aminoalkylsulfonic acids" page 683; column 2; XP002098857 see abstract & JP 60 023360 A (MITSUI TOATSU CHEMICALS, INC.) 5 February 1985	1
X	--- HANKOVSKY O.H. ET AL.: "New antiarrhythmic agents. 2,2,5,5-tetramethyl-3-pyrroline-3-carboxami des and 2,2,5,5-tetramethylpyrrolidine-3-carboxami des" JOURNAL OF MEDICINAL CHEMISTRY, vol. 29, no. 7, 1986, pages 1138-1152, XP002068557 see compound 1e see page 1141	1
X	--- SERGEEV G.B. & KOMAROV V.S.: "Organic reactions in the solid phase prepared by co-deposition of reagent vapours onto cold surface" MOLECULAR CRYSTALS AND LIQUID CRYSTALS (INC. NONLINEAR OPTICS), vol. 156, 1988, pages 129-138, XP002098854 see compound II see page 136	1
X	--- EP 0 506 532 A (LIPHA, LYONNAISE INDUSTRIELLE PHARMACEUTIQUE) 30 September 1992 see intermediate of compound 9 see claim 7, formula 5	1
X	--- O'BRIEN P.M. ET AL.: "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 8. Incorporation of amide or amine functionalities into a series of disubstituted ureas and carbamates. Effects on ACAT inhibition in vitro and efficacy in vivo" JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 12, 1994, pages 1810-1822, XP002082610 see scheme 5, compound 23d	1
X	--- EP 0 678 503 A (CIBA-GEIGY AG) 25 October 1995 see page 75, line 37; example 123 ---	1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 05201 A (BRITISH BIOTECH PHARMACEUTICALS) 22 February 1996 see claim 22(viii), formula XXI see example 11(b) ---	1
X	BELLEMIN R. ET AL.: "New indole derivatives as ACAT inhibitors: Synthesis and structure-activity relationships" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, CHIM. THER., vol. 31, no. 2, 1996, pages 123-132, XP004040099 see scheme 1, compound 2m see page 126; table II ---	1
X	LUCET D. ET AL.: "Highly stereoselective conjugate addition of (R)- or (S)-4-phenyl-2-oxazolidinone to nitroalkenes" JOURNAL OF ORGANIC CHEMISTRY, vol. 62, no. 9, April 1997, pages 2682-2683, XP002098855 see scheme 1, first formula see page 2683 ---	1
X	WHITLOCK G.A. & CARREIRA E.M.: "Enantioselective synthesis of ent-Stelletamide A via a novel dipolar cycloaddition reaction of (trimethylsilyl)diazomethane" JOURNAL OF ORGANIC CHEMISTRY, vol. 62, no. 23, November 1997, pages 7916-7917, XP002098856 see scheme 2, precursor of 17 see page 7917 ---	1
Y	KRAUS J.L.: "Isosterism and molecular modification in drug design: Tetrazole analogue of GABA: Effects on enzymes of the gamma.-aminobutyrate system" PHARMACOLOGICAL RESEARCH COMMUNICATIONS, vol. 15, no. 2, 1983, pages 183-189, XP002096228 see the whole document ---	1,3-7
Y	BURGER A.: "Isosterism and bioisosterism in drug design" PROGRESS IN DRUG DESIGN, vol. 37, 1991, pages 287-371, XP002096229 see page 332 - page 338 ---	1,3-7
Y	WO 92 09560 A (NORTHWESTERN UNIVERSITY) 11 June 1992 see the whole document ---	1,3-7

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KERR D.I.B. & ONG J.: "GABA agonists and antagonists" MEDICINAL RESEARCH REVIEWS, vol. 12, no. 6, 6 November 1992, pages 593-636, XP002080823 see page 620 - page 628 ---	1,3-7
Y	HOWSON W. ET AL.: "Biological activity of 3-aminopropyl (methyl) phosphinic acid, a potent and selective GABA(B) agonist with CNS activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 3, no. 4, 1993, pages 515-518, XP002096230 see the whole document ---	1,3-7
Y	PATANI G.A. & LA VOIE E.J.: "Bioisosterism: A rational approach in drug design" CHEMICAL REVIEWS, vol. 96, no. 8, 1996, pages 3147-3176, XP000652176 see 3. Carboxylate group bioisosteres see page 3168, left-hand column - page 3170, left-hand column ---	1,3-7
P,Y	WO 98 17627 A (WARNER-LAMBERT COMPANY) 30 April 1998 see the whole document -----	1,3-7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/23917

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8-18
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☒ Claims Nos.: 2
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
Dependent claim 2 defines an integer m , which appears neither in formula 1A nor in formula 1B.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/23917

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 2465803	A	29-03-1949	NONE	
US 2866786	A	30-12-1958	CH 325458 A DE 932676 C FR 1100176 A GB 752227 A	16-09-1955
EP 61673	A	06-10-1982	JP 1044188 B JP 1557669 C JP 58121278 A JP 1601704 C JP 2027992 B JP 58121279 A JP 1499131 C JP 57156463 A JP 63048869 B JP 1508507 C JP 57200366 A JP 63061942 B US 4456757 A US 4525589 A US 4560755 A	26-09-1989 16-05-1990 19-07-1983 27-02-1991 20-06-1990 19-07-1983 29-05-1989 27-09-1982 30-09-1988 26-07-1989 08-12-1982 30-11-1988 26-06-1984 25-06-1985 24-12-1985
EP 506532	A	30-09-1992	FR 2674522 A AT 111078 T AU 658609 B AU 1309492 A CA 2063170 A CS 9200895 A DE 69200378 D DE 69200378 T DK 506532 T ES 2064149 T HU 65489 A IE 65366 B IL 101248 A JP 5097802 A KR 9507753 B MX 9201365 A NO 178260 B NZ 242078 A OA 9573 A SI 9210305 A RU 2074179 C US 5219859 A ZA 9202163 A	02-10-1992 15-09-1994 27-04-1995 01-10-1992 27-09-1992 14-10-1992 13-10-1994 09-03-1995 20-02-1995 16-01-1995 28-06-1994 18-10-1995 05-12-1996 20-04-1993 14-07-1995 01-10-1992 13-11-1995 26-10-1994 31-01-1993 29-02-1996 27-02-1997 15-06-1993 27-09-1993
EP 678503	A	25-10-1995	AU 1642095 A AU 699616 B AU 1642195 A AU 1642395 A CA 2147044 A CA 2147052 A CA 2147056 A CN 1117960 A CZ 9500976 A EP 0678514 A EP 0678500 A	26-10-1995 10-12-1998 26-10-1995 26-10-1995 19-10-1995 19-10-1995 19-10-1995 06-03-1996 15-11-1995 25-10-1995 25-10-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/23917

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 678503	A		FI 951771 A	19-10-1995
			FI 951772 A	19-10-1995
			FI 951773 A	19-10-1995
			HU 74074 A	28-10-1996
			HU 72110 A	28-03-1996
			HU 71701 A	29-01-1996
			JP 8053434 A	27-02-1996
			JP 8081430 A	26-03-1996
			JP 8027079 A	30-01-1996
			NO 951441 A	19-10-1995
			NO 951442 A	19-10-1995
			NO 951443 A	19-10-1995
			NZ 270936 A	24-06-1997
			NZ 270938 A	26-11-1996
			NZ 270939 A	20-12-1996
			US 5606078 A	25-02-1997
			US 5659065 A	19-08-1997
			US 5559111 A	24-09-1996
			US 5654445 A	05-08-1997
			US 5646143 A	08-07-1997
			US 5627182 A	06-05-1997
			US 5705658 A	06-01-1998
			ZA 9503050 A	08-11-1995
			ZA 9503051 A	18-10-1995
			ZA 9503052 A	18-10-1995

WO 9605201	A	22-02-1996	AU 3186395 A	07-03-1996
			EP 0775139 A	28-05-1997
			US 5753671 A	19-05-1998

WO 9209560	A	11-06-1992	AU 9137091 A	25-06-1992
			MX 9102241 A	31-01-1994
			US 5563175 A	08-10-1996
			US 5684189 A	04-11-1997
			US 5608090 A	04-03-1997
			US 5599973 A	04-02-1997
			US 5710304 A	20-01-1998
			US 5847151 A	08-12-1998

WO 9817627	A	30-04-1998	AU 4669797 A	15-05-1998
			HR 970560 A	31-08-1998
